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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
50-783**

Chemistry Review(s)

DEC 27 2000

Division of Dermatological and Dental Drug Products, HFD-540

DMF: [] Type II

Title: Doxycycline Hyclate -

1. CHEM REVIEW No. 1

2. REVIEW DATE: 12-Dec-00

3. ITEM REVIEWED:

A. IDENTIFICATION

USAN: Doxycycline hyclate
Ingredient Dictionary Name: Doxycycline hydrochloride hemihydrate
hemethanolate.
Tradename: PerioStat
Manufacturer's Code: MA51
Chemical Name: [4S-(4 α ,4 α ,5 α ,5 α ,6 α ,12 α)]-4-(Dimethylamino)-
,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12-12a-pentahydroxy-6-
methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate.
CAS Number: 24390-14-5

B. LOCATION IN DMF

<u>Type of Submission</u>	<u>Date of Submission</u>	<u>Location of Information</u>
DMF Amendment	18-Feb-00	Vol.6.1, dated 2/18/00
DMF Amendment	02-Jun-99	Vol.6.1, dated 6/2/99

4. PREVIOUS DOCUMENTS

<u>Type of Document</u>	<u>Date of Document</u>	<u>Comment</u>
AADA 62-839 / S-008	08-Aug-96	Adequate Review

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:
ADDRESS:

REPRESENTATIVE or U.S. AGENT (if applicable):

NAME:
ADDRESS:

6. DMF REFERENCED FOR:

NDA/ANDA/SUPPLEMENT/IND: NDA 50-783
PRIMARY DMF (as needed):
APPLICANT NAME: CollaGenex Pharmaceuticals
LOA DATE: 06-Mar-00
DRUG PRODUCT NAME: PerioStat
DOSAGE FORM: Tablet CODE: 500
STRENGTH: 20 mg
ROUTE OF ADMINISTRATION: Oral CODE: 001

7. SUPPORTING DOCUMENTS: AADA 62-839/S-008, Dtd. 8/8/96
8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF: 14-Jul-00
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE BEEN PROVIDED: 07-Jul-00
10. CONSULTS: Not Applicable

11. COMMENTS:
The 6/2/99 & 2/18/00 amendments were reviewed. The former amendment referenced a quality system related to doxycycline hyclate manufacturing. The latter reviewed [redacted] as an additional supplier of [redacted]. Both amendments were adequate, however, the latter has an IR.

12. CONCLUSIONS:
This review of DMF [redacted] found both the 6/2/99 and 2/18/00 amendments to be ADEQUATE.

However, there is an Informational Request in the 2/18/00 amendment for comparative physical studies to be conducted on the doxycycline hyclate synthesized by each of the [redacted] and [redacted].

[redacted] S/ 12/13/00
James D. Vidra, Ph.D.
Review Chemist
HFD-830/HFD-540

[redacted] S/ 12/27/00
Wilson H. DeCamp, Ph.D.
Chemistry Team Leader
HFD-830/HFD-540

cc:

DMF [redacted] (2copies)
HFD-540/Div File NDA 50-783
HFD-540/ProjMgr/Cross
HFD-540/ChmTL/DeCamp
R/D Init by JD Vidra

File: Dm [redacted]

Redacted 17.

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HFD 540
CROSS

JAN 10 2001

Division of Dermatological and Dental Drug Products, HFD-540

DMF Number [redacted] DMF Type II:
Title: [redacted] Amendment 90

1. **CHEM REVIEW No.** 56

2. **REVIEW DATE:** January 4, 2001

3. **ITEM REVIEWED:**

A. **IDENTIFICATION**

USAN: Not Applicable

Ingredient Dictionary Name: Not Applicable

Tradename:

Manufacturer's Code:

Chemical Name: Not Applicable

CAS Number: Not Applicable

B. **LOCATION IN DMF**

<u>Type of Submission</u>	<u>Date of Submission</u>	<u>Location of Information</u>
Amendment 90	17-Apr-00	Vol. 6.1
Amendment 90	07-Dec-99	Vol. 5.1

4. **PREVIOUS DOCUMENTS**

<u>Type of Document</u>	<u>Date of Document</u>	<u>Comment</u>
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5. **NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):**

NAME:

ADDRESS:

CONTACT PERSON'S NAME:

TITLE, DEPARTMENT:

ADDRESS:

TELEPHONE:

Same as above.

6. **DMF REFERENCED FOR:**

NDA/ANDA/IND:

NDA 50-783

PRIMARY DMF (as needed):

Not Applicable

APPLICANT NAME:

CollaGenex Pharmaceuticals

LOA DATE:

March 7, 2000

DRUG PRODUCT NAME:

PerioStat

DOSE FORM:

Tablet

CODE: 500

STRENGTH:

20 mg

ROUTE OF ADMINISTRATION:

Oral

CODE: 001

7. **SUPPORTING DOCUMENTS:**

Amendment

22-Feb-00

Update of Authorized Companies

DMF [redacted]

Page 2 of 5

8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF: 22-Dec-00
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE
BEEN PROVIDED: 22-Feb-00
9. CONSULTS: Not Applicable
10. COMMENTS:
Two Amendment 90s on [redacted] were reviewed and found ADEQUATE.
11. CONCLUSIONS: ADEQUATE.

[Signature] /S/ 1/4/01
James D. Vidra, Ph.D.

Review Chemist, HFD-830/HFD-540

[Signature] /S/ 1/4/01
Wilson H. DeCamp, Ph.D.

Chemistry Team Leader, HFD 830/HFD-540

Attachments (3)

cc:

DMF [redacted] (2 copies)

HFD-540/Division File for NDA 50-783/000

HFD-540/Chm/Vidra

HFD-540/PM/Cross

HFD-540/ChmTL/DeCamp

R/D Init by: Vidra

File: DMF [redacted]

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JAN 10 2001

Division of Dermatological and Dental Drug Products, HFD-540

DMF: [] DMF Type: III

Title: []

1. CHEM REVIEW No. 5

2. REVIEW DATE: 08-Jan-01

3. ITEM REVIEWED:

A. IDENTIFICATION

USAN:

Not Applicable

Ingredient Dictionary Name:

Not Applicable

Tradename:

Manufacturer's Code:

Chemical Name:

Not Applicable

CAS Number:

Not Applicable

B. LOCATION IN DMF

Type of Submission

Date of Submission

Location of Information

Amendment

21-Jan-00

Vols. 2.1 - 2.4

4. PREVIOUS DOCUMENTS

Type of Document

Date of Document

Comment

Review

13-Apr-00

Adequate for []

Review

26-Apr-00

Adequate for []

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:

ADDRESS:

CONTACT PERSON'S NAME:

ADDRESS:

TELEPHONE:

Same as above.

6. DMF REFERENCED FOR:

NDA/ANDA/SUPPLEMENT/IND: NDA 50-783/000

PRIMARY DMF (as needed):

Not Applicable

APPLICANT NAME:

CollaGenex Pharmaceuticals, Inc.

LOA DATE:

February 14, 2000

DRUG PRODUCT NAME:

PerioStat

DOSAGE FORM:

Tablet

CODE: 500

STRENGTH:

20 mg

ROUTE OF ADMINISTRATION:

Oral

CODE: 001

10

7. SUPPORTING DOCUMENTS: None
8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF: January 21, 2000
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA'S HAVE
BEEN PROVIDED: January 21, 2000
9. CONSULTS: Not Applicable
10. COMMENTS: ADEQUATE for [REDACTED]
[REDACTED]
11. CONCLUSIONS: ADEQUATE

[REDACTED] 1/10/01
James D. Vidra, Ph.D.
Review Chemist, HFD-540/HFD-830

[REDACTED] 1/10/01
Wilson H. DeCamp, Ph.D.
Review Chemist, HFD-540/HFD-830

Attachments (3)

Cc: DMF [REDACTED] (2 copies)
HFD-540/DivFile NDA 50-783
HFD-540/PrjMgt/Cross
HFD-540/Chm/Vidra
HFD-540/ChmTL/DeCamp

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DIVISION OF DERMATOLOGICAL AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-783/000 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 12-Jan-01

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	31-Mar-00	04-Apr-00	10-Apr-00
Amendment BC	17-Apr-00	18-Apr-00	02-May-00
Amendment XR	20-Apr-00	21-Apr-00	NAI on 09-May-00
Amendment BC	24-Apr-00	25-Apr-00	01-May-00
Amendment BC	11-Oct-00	12-Oct-00	18-Oct-00
Amendment BC	19-Dec-00	20-Dec-00	29-Dec-00
Amendment BC	05-Jan-01	09-Jan-01	09-Jan-01
Amendment BC	10-Jan-01	11-Jan-01	11-Jan-01

NAME & ADDRESS OF APPLICANT:

CollaGenex Pharmaceuticals, Inc.
41 University Drive
Newtown, Pennsylvania 18940
ATTN: Christopher Powala
Senior Director
Drug Development &
Regulatory Affairs
Telephone No. (215) 579-7388
Fax No. (215) 579-8577

DRUG PRODUCT NAME

<u>Proprietary:</u>	PerioStat
<u>Nonproprietary/USAN:</u>	Doxycycline Hyclate
<u>Code Names/#'s:</u>	Doxycycline Hydrochloride
	Hemihydrate hemeiethanolate
<u>Chemical Type/</u>	Antibiotic
<u>Therapeutic Classes:</u>	3S

ANDA Suitability Petition/DESI/Patent Status: NOT APPLICABLE!

PHARMACOLOGICAL CATEGORY/INDICATION: Treatment of Adult Periodontitis

<u>DOSAGE FORM:</u>	Tablet
<u>STRENGTHS:</u>	20 mg
<u>ROUTE OF ADMINISTRATION:</u>	Oral
<u>DISPENSED:</u>	Rx <u>X</u> OTC <u> </u>

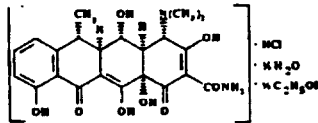
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,

MOL.WT:

4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride with ethyl alcohol (2:1) monohydrate.

Molecular Weight: 1025.89

PerioStat (doxycycline hyclate) Tablet, 20 mg

Molecular Formula: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_5OH \cdot 1/2H_2O$ **Structural Formula:**

doxycycline hyclate

SUPPORTING DOCUMENTS:

Type / Number	Subject	Holder	Status	Review Date	Letter Date
Type II DMF [redacted]	[redacted]	[redacted]	Adequate	1/3/01	3/6/00
Type III DMF [redacted]			Adequate	4/20/00	2/22/00
Type III DMF [redacted]			Adequate	1/4/01	3/7/00
Type III DMF [redacted]			Adequate	12/19/00	3/17/00
Type III DMF [redacted]			Both Adequate	o 1g, 4/13/00 o 3g, 1/8/01	o 1g LOA on 2/14/00 o 3g LOA on 2/14/00
Type III DMF [redacted]			Adequate	9/21/99	3/21/00
Type IV DMF [redacted]			Adequate	2/28/00	8/23/00
NDA 50-744	PerioStat Capsules	CollaGenex Pharmaceuticals, Inc.	Approved	9/30/98	NA

REMARKS/COMMENTS:

The PerioStat Tablet is similar to the previously approved PerioStat Capsules (NDA 50-744 approved on 9/30/98) with respect to drug substance concentration and labeling. The clinical indication also remains the same, e.g., for the treatment of adult periodontitis. No additional clinical studies were conducted with the PerioStat Tablets, only bioequivalence studies to demonstrate equivalence with the previous PerioStat Capsules. Most of the tablet ingredients are similar to the capsule ingredients with the exception of the tablet film coating [redacted] which was reviewed in Type IV DMF [redacted] and found adequate. The major CMC factors to be reviewed in NDA 50-783 include the tablet film coating, the dissolution rate of the tablet (primarily a biopharmaceutical function), the length of stability data for the new drug product, additional product quality tests and the new container closure systems.

PerioStat (doxycycline hyclate) Tablet, 20 mg

The PerioStat Tablets will be sampled in a [redacted] Blister Card of eight tablets and commercialized in 120 cc white [redacted] square bottles containing 60 tablets and in 325 cc [redacted] bottles containing 1,000 tablets. Each of the two bottle also contains a desiccant, [redacted] and a child-resistant white plastic cap with liner.

The drug substance, doxycycline hyclate, was upgraded into a new DMF format from its previous AADA format involving many minor areas. A new supplier, [redacted] was identified that manufactured [redacted] is one of two possible starting materials used in the synthesis of doxycycline hyclate. Drug Master File # [redacted] was found adequate for these drug substance changes.

The two manufacturers and packager were prepared for inspection and found acceptable.

CONCLUSIONS & RECOMMENDATIONS:

NDA 50-783/000 is Recommended for Approval.

/s/

James D. Vidra, Ph.D.
Review Chemist

cc: Orig. NDA# 50-783
HFD-540/Division File
HFD-540/DO/Kelsey
HFD-540/PharmTox/See
HFD-540/ProjMan/Cross
HFD-540/Chem/Vidra
HFD-540/TeamLdr/DeCamp

filename: N50783.000

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